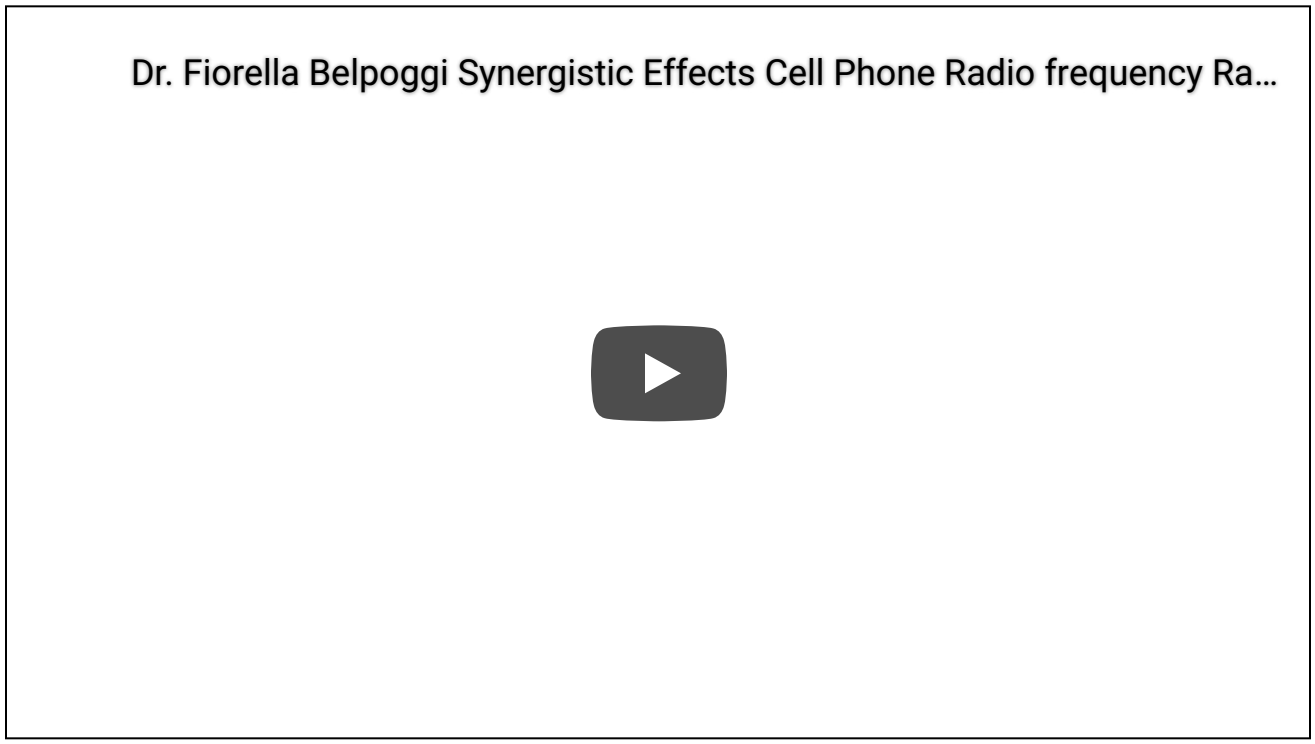
Recent Studies Showing Synergistic Effects



Kostoff, R.N. and Clifford G.Y. Lau. 2017. **"Modified health effects of non-ionizing electromagnetic radiation combined with other agents reported in the biomedical literature."** *Microwave Effects on DNA and Proteins* (2017): 97-158.

- The present chapter examines the scope of non-ionizing EMF radiation combined effects; i.e., identifies effects on biological systems from combined exposure to non-ionizing electromagnetic fields/radiation and at least one other agent.

Soffritti M, Giuliani L. **The carcinogenic potential of non-ionizing radiations: The cases of S-50 Hz MF and 1.8 GHz GSM radiofrequency radiation.** *Basic Clin Pharmacol Toxicol*.

2019;125 Suppl 3:58-69. doi:10.1111/bcpt.13215

- Four large life-span carcinogenic bioassays conducted on over 7000 Sprague Dawley rats exposed from prenatal life until natural death to S-50 Hz MF alone or combined with gamma radiation or formaldehyde or aflatoxin B1.
- Results now available from these studies, which started concurrently, have shown that exposure to Sinusoidal-50 Hz Magnetic Field (S-50 Hz MF) combined with acute exposure to gamma radiation or to chronic administration of formaldehyde in drinking water induces a significantly increased incidence of malignant tumours in males and females.
- A second project of two large life-span carcinogenic bioassays was conducted on over 3000 Sprague Dawley rats exposed from prenatal life until natural death to 1.8 GHz GSM of mobile phone radio base station, alone or combined with acute exposure to gamma radiation. Early results from the experiment on 1.8 GHz GSM alone show a statistically significant increase in the incidence of heart malignant schwannoma among males exposed at the highest dose.
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Soffritti, Morando, et al. "Synergism between sinusoidal-50 Hz magnetic field and formaldehyde in triggering carcinogenic effects in male Sprague–Dawley rats." *American Journal of Industrial Medicine* 59.7 (2016) 509-21.

- The objective of this study was to evaluate the potential synergistic carcinogenic effects of concurrent exposure to ELF MF and formaldehyde in four groups of male and female Sprague–Dawley rats. Results showed that compared to untreated controls, life-span exposure to MF and formaldehyde induced statistically significant carcinogenic effects in male rats.

Soffritti, Morando, et al. "Life-span exposure to sinusoidal-50 Hz magnetic field and acute low-dose γ radiation induce carcinogenic effects in Sprague-Dawley rats." *International Journal of Radiation Biology* 92.4 (2016): 202-14.

- The present study examined the carcinogenic effects of combined exposure to sinusoidal-50 Hz (S-50Hz) magnetic fields and acute γ radiation in Sprague-Dawley rats. The results of the study showed significant carcinogenic effects for the mammary gland in males and females and a significant increased incidence of malignant schwannomas of the heart as well as increased incidence of lymphomas/leukemias in males.

Tang, J., et al. "Exposure to 900 MHz electromagnetic fields activates the mkp-1/ERK pathway and causes blood-brain barrier damage and cognitive impairment in rats." *Brain Research* 1601 (2015): 92-101.

- This study demonstrated, for the first time, the blood-brain barrier and cognitive changes in rats exposed to 900 MHz electromagnetic field (EMF) and aims to elucidate the potential molecular pathway underlying these changes. Researchers found that EMF exposure for 28 days induced the expression of mkp-1, resulting in ERK dephosphorylation. Taken together, these results demonstrated that exposure to 900 MHz EMF radiation for 28 days can significantly impair spatial memory and damage BBB permeability in rat by activating the mkp-1/ERK pathway.

Dockrill, Peter. "Scientists have Breached the Blood-Brain Barrier for the First Time to Treat a Brain Tumor." *Science Alert* (2015).

- Sunnybrook scientists were able to use MRI-guided focused low-intensity ultrasound (sound waves) to breach the blood-brain barrier and more effectively deliver chemotherapy into the brain tumour of a patient.

Zhang, Feng, Chun-Lei Xu and Chun-Mei Liu. "Drug delivery strategies to enhance the permeability of the blood–brain barrier for treatment of glioma." *Drug Design, Development and Therapy* 9 (2015): 2089-100.

- This review highlights the innovative technologies that have been introduced to enhance the permeability of the BBB and to obtain an optimal distribution and concentration of drugs in the brain to treat gliomas, such as nanotechniques, hyperthermia techniques, receptor-mediated transport, cell-penetrating peptides, and cell-mediated delivery.

Lerchl, Alexander, et al. "Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans." *Biochemical and Biophysical Research Communications* 459.4 (2015): 585-90.

- Researchers performed a replication study of previously published results with carcinogen-treated mice which suggested tumor-promoting effects of RF-EMF (Tillmann et al., 2010). Authors confirmed and extended the originally reported findings. Numbers of tumors of the lungs and livers in exposed animals were significantly higher than in sham-exposed controls. In addition, lymphomas were also found to be significantly elevated by exposure.

Turner, M. C., et al., "Occupational exposure to extremely low-frequency magnetic fields and brain tumor risks in the INTEROCC study." *Cancer Epidemiology Biomarkers and Prevention* 23.9 (2014): 1863–72.

- This study examines the association between ELF and brain tumours in the large-scale INTEROCC study. Results showed positive associations between ELF in the recent past and glioma indicating that occupational ELF exposure may play a role in the later stages (promotion and progression) of brain tumourigenesis.

Vila et al., **Occupational exposure to high-frequency electromagnetic fields and brain tumor risk in the INTEROCC study: An individualized assessment approach,** Environ Int. 2018 Oct;119:353-365. doi: 10.1016/j.envint.2018.06.038. Epub 2018 Jul 8.

- "The largest adjusted ORs were obtained for cumulative exposure to RF magnetic fields (as A/m-years) in the highest exposed category (≥90th percentile) for the most recent exposure time window (1-4 years before the diagnosis or reference date) for both glioma, OR = 1.62 (95% confidence interval (CI): 0.86, 3.01) and meningioma (OR = 1.52, 95% CI: 0.65, 3.55)."
- "the results obtained for recent exposure to RF electric and magnetic fields are suggestive of a potential role in brain tumor promotion/progression and should be further investigated."

Omar, Ayman I. "Tumor Treating Field Therapy in Combination with Bevacizumab for the Treatment of Recurrent Glioblastoma." *Journal of Visualized Experiments* 92.e51638 (2014).

- Here we describe a novel approach for the treatment of recurrent glioblastoma using the delivery of both TTFields as well as the simultaneous bevacizumab infusion. This novel TTF system is an FDA approved device that delivers intermediate frequency, low intensity alternating electric field directly to the brain for the treatment of recurrent glioblastomas

Byun, Yoon-Hwan, et al. "Mobile Phone Use, Blood Lead Levels, and Attention Deficit Hyperactivity Symptoms in Children: A Longitudinal Study. *PLoS ONE* 8.3 (2013).

- The purpose of this longitudinal study was to investigate the association between mobile phone use and symptoms of Attention Deficit Hyperactivity Disorder (ADHD) considering the modifying effect of lead exposure. The results suggest that simultaneous exposure to lead and RF from mobile phone use was associated with increased ADHD symptom risk.

Kostoff, Ronald N. and Clifford G.Y. Lau. "Combined biological and health effects of electromagnetic fields and other agents in the published literature." ***Technological Forecasting and Social Change*** **80.7 (2013): 1331-1349.**

- The present study examines the scope of the combined effects of electromagnetic field radiation; i.e., identify effects on biological systems from combined exposure to electromagnetic fields/radiation and at least one other agent. Beneficial effects include improved treatment of chronic diseases like cancer by enhancing ionizing radiation or chemotherapy, and accelerated healing of wounds and injuries in concert with other agents. Adverse effects, on the other hand, include enhanced carcinogenesis, cellular or genetic mutations, and teratogenicity.

Tillmann, Thomas, et al. "Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model." ***International Journal of Radiation Biology*** **86.7 (2010): 529–41.**

- The purpose of this study was to evaluate putative effects on tumour susceptibility in mice exposed to a UMTS (universal mobile telecommunications system) test signal for up to 24 months, commencing with embryo-fetal exposure. This pilot study indicates a co-carcinogenic effect of lifelong UMTS exposure (4.8 W/m2) in female B6C3F1 descendants subjected to pretreatment with ethylnitrosourea.

Nittby, Henrietta, et al. "Increased blood–brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone." ***Pathophysiology*** **16.2-3 (2009): 103-12.**

- The present findings are in agreement with our earlier studies where we have seen increased BBB permeability immediately and 14 days after exposure to electromagnetic radiation emitted by mobile phones. We here discuss the present findings as well as the previous results of altered BBB permeability from our and other laboratories.

Eberhardt, Jacob L., et al. "Blood-Brain Barrier Permeability and Nerve Cell Damage in Rat Brain 14 and 28 Days After Exposure to Microwaves from GSM Mobile Phones." ***Electromagnetic Biology and Medicine*** **27.3 (2008): 215-29.**

- We investigated the effects of global system for mobile communication (GSM) microwave exposure on the permeability of the blood-brain barrier and signs of neuronal damage in rats using a real GSM programmable mobile phone in the 900 MHz band. Albumin extravasation and also its uptake into neurons was seen to be enhanced after 14 d, but not after a 28 d recovery period. The occurrence of dark

neurons in the rat brains, on the other hand, was enhanced later, after 28 d ($p = 0.02$). Furthermore, in the 28-d brain samples, neuronal albumin uptake was significantly correlated to occurrence of damaged neurons.

Nittby, Henriettta, et al. "Radiofrequency and Extremely Low-Frequency Electromagnetic Field Effects on the Blood-Brain Barrier." *Electromagnetic Biology and Medicine* 27.2 (2008): 103-126.

- There is evidence that exposure to electromagnetic fields at non thermal levels disrupts this barrier. In this review, the scientific findings in this field are presented. The result is a complex picture, where some studies show effects on the blood-brain barrier, whereas others do not. Possible mechanisms for the interactions between electromagnetic fields and the living organisms are discussed.

Tillmann Thomas, et al. "Carcinogenicity study of GSM and DCS wireless communication signals in B6C3F1 mice." *Bioelectromagnetics* 28.3 (2007): 173–87.

- The purpose of this study using a total of 1170 B6C3F1 mice was to detect and evaluate possible carcinogenic effects in mice exposed to radio-frequency-radiation (RFR) from Global System for Mobile Communication (GSM) and Digital Personal Communications System (DCS) handsets. The present study produced no evidence that the exposure of male and female B6C3F1 mice to wireless GSM and DCS radio frequency signals at a whole body absorption rate of up to 4.0 W/kg resulted in any adverse health effect or had any cumulative influence on the incidence or severity of neoplastic and non-neoplastic background lesions, and thus the study did not provide any evidence of RF possessing a carcinogenic potential.

Belyaev, I.Y., et al. "Exposure of rat brain to 915 MHz GSM microwaves induces changes in gene expression but not double stranded DNA breaks or effects on chromatin conformation." *Bioelectromagnetics* 27.4 (2006): 295-306.

- We investigated whether exposure of rat brain to microwaves (MWs) of global system for mobile communication (GSM) induces DNA breaks, changes in chromatin conformation and in gene expression. The data shows that GSM MWs at 915 MHz did not induce PFGE-detectable DNA double stranded breaks or changes in chromatin conformation, but affected expression of genes in rat brain cells.

Ruiz-Gomez, M.J. and M. Martinez-Morillo. "Enhancement of the cell-killing effect of ultraviolet-C radiation by short-term exposure to a pulsed magnetic field." *International Journal of Radiation Biology* 81.7 (2005): 483-90.

- The purpose of this study was to investigate whether low frequency pulsed magnetic field (PMF) exposures produce alterations in the cell killing induced by ultraviolet C (UVC) radiation. Results show that PMF in combination with UVC have the ability to augment the cell killing effects of UVC radiation. In addition, the effects appear to be greater when PMF and UVC are applied at the same time.

Leszczynski, D., et al. "Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in human endothelial cells: molecular mechanism for cancer- and blood-brain barrier-related effects." *Differentiation* 70.2-3 (2002): 120-9.

- Researchers examined whether non-thermal exposures of cultures of the human endothelial cell line EA.hy926 to 900 MHz GSM mobile phone microwave radiation could activate stress response. Results obtained demonstrate that 1-hour non-thermal exposure of EA.hy926 cells changes the phosphorylation status of numerous, yet largely unidentified, proteins. We postulate that these events, when occurring repeatedly over a long period of time, might become a health hazard because of the possible accumulation of brain tissue damage. Furthermore, our hypothesis suggests that other brain damaging factors may co-participate in mobile phone radiation-induced effects.

Lai, Henry. "Neurological Effects of Radiofrequency Electromagnetic Radiation Relating to Wireless Communication Technology." Paper presented at the IBC-UK Conference: "Mobile Phones – Is there a Health Risk?" September 16-17, 1997.

- The following is a brief summary of scientific research on the effects of RFR exposure on the nervous system.

Salford, L.G., et al. "Permeability of the blood-brain barrier induced by 915 MHz electromagnetic radiation, continuous wave and modulated at 8, 16, 50, and 200 Hz." *Microscopy Research and Technique* 27.6 (1994): 535-42.

- In the present investigation we exposed male and female Fischer 344 rats in a transverse electromagnetic transmission line chamber to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated with repetition rates of 8, 16, 50, and 200 s-1. The results show albumin leakage in 5 of 62 of the controls and in 56 of 184 of the animals exposed to microwaves.

Persson, Bertil R.R., et al. "Increased Permeability of the Blood-Brain Barrier Induced by Magnetic and Electromagnetic Fields." *Biological Effects and Safety Aspects of Nuclear Magnetic Resonance Imaging and Spectroscopy* 649 (1992): 356-8.

- Researchers studied the permeability of the blood-brain barrier after exposure to the components of the MRI electromagnetic fields: static magnetic fields, low frequency pulsed magnetic fields, radio-frequency electromagnetic fields, and a combination of these three types of fields. Authors concluded that radio-frequency radiation has the effects of increasing the permeability of the BBB.

Szmigielski, S., et al. "Accelerated development of spontaneous and benzo-pyrene-induced skin cancer in mice exposed to 2450- MHz microwave radiation." *Bioelectromagnetics* 3.2 (1982): 179–91.

- Microwave-exposed C3H/HeA mice developed breast tumors earlier than controls. A similar acceleration was observed in the development of BP-induced skin cancer in mice exposed simultaneously to BP and MWs. The acceleration of cancer development in all tested systems and lowering of natural antineoplastic resistance was similar in mice exposed to MW at 5 mW/cm2 or to chronic stress caused by confinement but differed significantly from the data obtained on animals exposed at 15 mW/cm2, where local thermal effects ("hot" spots) were possible.

Szudziński, A., et al. "Acceleration of the development of benzopyrene- induced skin cancer in mice by microwave radiation." *Arch Dermatol Res* 274.3-4 (1982): 303–12.

- In the present study Balb/c mice were exposed to chemical carcinogen, 3,4-benzopyrene and simultaneously irradiated with athermal (5 mW/cm2) or subthermal (15 mW/cm2) doses of 2,450 MHz microwaves. All protocols of microwave irradiations resulted in a significant acceleration of the development of benzopyrene-induced skin cancer and in shortening of life span of the tumour-bearing hosts. It is suggested that the observed co-carcinogenic effect of microwave radiation may, at least in part, result from the inhibitory action of microwaves on cellular immune reactions of exposed animals.

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